

Attorney Docket No.: **UMD0067US.NP**  
Inventors: **Welsh et al.**  
Serial No.: **10/565,417**  
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**REMARKS**

Claims 1-8 are pending in the instant application. Claims 1-8 have been rejected. Claims 1-4 have been amended. Claims 5-8 have been canceled. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of these amendments and the following remarks.

**I. Objection to the Title of the Invention**

The title of the invention has been objected to. The Examiner suggests that a new title is required that is clearly indicative of the invention to which the claims are drawn. To facilitate the prosecution of this application, Applicants have amended to the title of the invention to read "Method of Imputing Missing Values in Microarray Data." Support for this amendment is found in claim 1 as originally filed. In light of this amendment, it is respectfully requested that this objection be withdrawn.

**II. Objection to the Specification**

The specification has been objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants have removed reference to the embedded hyperlink and therefore respectfully request that this objection be withdrawn.

**III. Rejection of the Claims Under 35 U.S.C. §101**

Claims 1-6 have been rejected under 35 U.S.C. 101 because it is suggested that the claimed invention is directed to non-statutory subject matter. It is suggested that the instant claims do not produce a tangible result and must set forth a practical

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application of the computational steps to produce a real-world result. Moreover, it is suggested that data structures not claimed as embodied in computer-readable media are descriptive material per se and not statutory. The Examiner suggests that the rejection of the method claims could be overcome by amending the claims to recite that the result of the method is outputted to a display or a memory, or by including a physical transformation. In the interest of facilitating the prosecution of this application, Applicants have amended claim 1 to indicate that the result is outputted to a display or memory as supported by the disclosure at the paragraph spanning pages 21-22. Furthermore, claims 3-4 have been amended to read on a computer-readable medium encoded with a computer program and claims 5-8 have been canceled. Support for this amendment is found at page 19, lines 14-28. In light of these amendments, it is respectfully requested that this rejection be withdrawn.

#### **IV. Rejection of Claims Under 35 U.S.C. §112**

Claims 1-8 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite. It is suggested that claims 1, 2, 4, 6, and 8 are vague and indefinite because the abbreviations "GMCimpute" and "K" are unclear. The Examiner suggests amending the claims to recite the full name in parentheses. Applicants have amended the claims to indicate that "GMC" refers to "Gaussian mixture clustering" as supported by the disclosure at page 11 (lines 1-2), and "K" refers to "number of clusters" as supported by the disclosure at page 6 (lines 28-29).

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Claims 2, 4, 6, and 8 have been further rejected under 35 U.S.C. 112, second paragraph, because it is suggested that there is insufficient antecedent basis for the limitation "row" in line 4 of these claims. Applicants have amended the rejected claims to clarify that a value of  $K$  is determined for microarray data comprising rows and columns, wherein the rows of the microarray data are subsequently partitioned into  $K$  partitions. Support for this amendment is found at page 15, lines 3-20, which teaches that the microarrays are composed of rows and columns.

In light of these amendments, it is respectfully requested that these rejections be withdrawn.

#### **V. Rejection of Claims Under 35 U.S.C. §102**

Claims 1-8 have been rejected under 35 U.S.C. 102(b) as being anticipated by Troyanskaya et al. ((2001) *Bioinformatics* 17:520-525) with additional support from online Merriam-Webster Dictionary ("Gaussian" definition). It is alleged that Troyanskaya et al. disclose methods for estimating missing values in DNA microarrays via imputing. The Examiner suggests that Troyanskaya et al. disclose k-means clustering and various model-based approaches and algorithms, such as SVDimpute algorithm via normalization. It is suggested that the online Merriam- Webster dictionary provides the definition of "Gaussian" as "being or having the shape of a normal curve or a normal distribution". Troyanskaya et al. is suggested to disclose using k eigengenes, using a row average, and an expectation maximization method that is repeated until the change falls below a threshold. It is also suggested that Troyanskaya et

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al. disclose software and methods implemented on a computer, which represents a computer program product and program and computer which inherently contains memory.

Claims 1, 3, 5, and 7 have been rejected under 35 U.S.C. 102(a) as being anticipated by Hytopoulos et al. (US 2002/0169560 A1) with additional support from online Merriam-Webster dictionary ("Gaussian" definition). It is alleged that Hytopoulos et al. disclose a computer-implemented method and a system using microarray expression data arrays, cluster arrays, and clustering tools, wherein the expression values have been normalized, filtered, and imputed, wherein missing data are imputed. It is suggested that the online Merriam-Webster dictionary provides the definition of "Gaussian" as "being or having the shape of a normal curve or a normal distribution", wherein the normalization of data represents normal distributions or Gaussian distributions or models. It is suggested that Hytopoulos et al. disclose using a computer readable medium in association with a computer including a processor and memory and computer instructions which are configured to cause a computer to process data, which represents an algorithm and computer software program and product. The Examiner suggests that Hytopoulos et al. disclose allowing the user to select K-nearest neighbor imputation mechanism or other data imputation mechanisms, the analysis of gene expression data to form clusters, and identifying genes represented in respective rows which represents a partitioning of rows of microarray data. It is further suggested that this reference discloses mapping rows of expression data and therefore anticipates the present invention.

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Applicants respectfully disagree and traverse these rejections.

At the outset, it is respectfully pointed out that the normalization described in by Troyanskaya et al. and Hytopoulos et al. refers to a different process in microarray data analysis. In the context of the teachings of the cited references, "normalization" transforms the data from different microarray chips into comparable magnitude and spread. These references do not teach or suggest that the data is transformed into one normal distribution. In contrast, the instant method employs Gaussian mixture clustering which imposes a mixture of multivariate normal (Gaussian) distributions (see pages 11-15). Therefore, the instant method is distinct from the teachings of Troyanskaya et al. and Hytopoulos et al.

To anticipate a claim "every element of the claimed invention must be identically shown in a single reference." *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). Because Troyanskaya et al. and Hytopoulos et al. fail to teach or suggest a Gaussian mixture clustering method, wherein each component is modeled by a multivariate normal distribution, these references cannot be held to anticipate the subject matter of the present invention. It is therefore respectfully requested that these rejections under 102(a) and 102(b) be reconsidered and withdrawn.

#### **VI. Rejection of Claims Under 35 U.S.C. §103**

Claims 2, 4, 6, and 8 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Hytopoulos et al. (US

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2002/0169560 A1) with additional support from online Merriam-Webster dictionary ("Gaussian" definition) as applied to claims 1, 3, 5, and 7 above, and further in view of Cereghini et al. (US 6,496,834 B1). It is suggested that Hytopoulos et al. describe the limitations in instant claims 1, 3, 5, and 7, as discussed above in the 35 USC 102 rejection. The Examiner acknowledges that Hytopoulos et al. do not describe repeating a classification expectation-maximization algorithm until the K partitions converge; however, Cereghini et al. describe a method of performing cluster analysis inside a relational database management system using Gaussian mixture parameters and implementing an Expectation-Maximization (EM) clustering algorithm iteratively. It is suggested that Cereghini et al. describe grouping a set of data into k clusters with k rows and that the expectation-maximization algorithm converges quickly. It is suggested that Hytopoulos et al. state that effective mechanisms for analyzing DNA array data are needed to determine which genes or combination of genes are correlated to various human conditions and that the EM algorithm is robust for noisy data and missing information. Cereghini et al. is suggested to indicate that cluster analysis does not typically work well with large databases due to memory limitations and the execution times required. In light of this, the Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use effective means for analyzing DNA array data, as stated by Hytopoulos et al., by using algorithms supporting large databases, as stated by Cereghini et al. It is suggested that the person of ordinary skill in the art would have been motivated to make that modification in order to find effective

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ways (as stated by Hytopoulos et al. and Cereghini et al.) of correlating genes to human conditions by allowing non-statisticians to benefit from advanced mathematical techniques available in a relational environment, as stated by Cereghini et al. Applicants respectfully disagree and traverse this rejection.

The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966), stated that three factual inquiries underpin any determination of obviousness, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved.

As discussed above, the "normalization" disclosed by Hytopoulos et al. refers to transformation of data from different microarray chips into comparable magnitude and spread, and does not refer to the Gaussian mixture cluster method of the present invention. Similarly, Cereghini et al did not use the Gaussian mixture cluster to estimate the missing values. Therefore, the combined teachings of these references do not teach or suggest each element of the claimed invention. Therefore, the cited prior art references cannot be held to make the present invention obvious under 35 U.S.C. 103(a). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

## **VII. Conclusion**

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

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favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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